ORIGINAL ARTICLE

Relative survival and quality of life benefits of pancreas–kidney transplantation, deceased kidney transplantation and dialysis in type 1 diabetes mellitus—a probabilistic simulation model

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SUMMARY

For patients with type 1 diabetes mellitus who progress to the point of requiring renal replacement therapy, the relative benefits of simultaneous pancreas and kidney transplantation (SPK) and deceased donor kidney transplantation across different age categories compared to dialysis are uncertain. Using Australian and New Zealand registry data from 2006 to 2016, a probabilistic Markov model (n = 10 000) was built comparing patient survival between SPK and deceased donor kidney transplantation with dialysis. Compared to dialysis, the average life years saved (LYS) and quality-adjusted life years (QALY) for SPK and deceased donor kidney transplantation were 5.48 [95% CI 5.47, 5.49] LYS and 6.48 [6.47, 6.49] QALY, and 3.38 [3.36, 3.40] LYS and 2.46 [2.45, 2.47] QALY, respectively. For recipients aged 50 years or younger, receiving a deceased donor kidney, the average incremental gains compared to dialysis were 4.13 [4.10, 4.16] LYS and 2.99 [2.97, 3.01] QALY, and for recipients older than 50 years, 3.05 [3.02, 3.08] LYS and 2.25 [2.23, 2.27] QALY. Compared to dialysis, SPK transplantation incurs the greatest benefits in LYS and QALY for patients with type 1 diabetes requiring renal replacement therapy. Patients older than 50 years still experience survival benefits from deceased donor kidney transplantation compared to dialysis.

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Key words
kidney transplantation, quality of life, SPK survival, type 1 diabetes

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Introduction

The prevalence of type 1 diabetes mellitus is increasing worldwide [1,2]. As of 2014, an estimated 387 million people have diabetes worldwide, of which type 1 diabetes accounts for between 5% and 10% [1]. One of the most frequent and serious complications associated with type 1 diabetes is diabetic nephropathy because of its association with hypertension, albuminuria and, ultimately, advanced stage kidney disease requiring renal replacement therapy [3]. Given its significant disease burden, there is a need to determine the optimal

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treatment strategy for patients type 1 diabetes mellitus who progress to end-stage kidney disease (ESKD). Current solid organ transplant options include kidney transplantation alone (from either a live or a deceased donor), simultaneous pancreas and kidney transplantation (SPK), or pancreas after kidney transplantation (PAK). Of these, SPK is an established treatment for patients with type 1 diabetes mellitus who progress to the point of requiring renal replacement therapy [4], because it improves survival and overall quality of life compared to being on dialysis [5,6]. The improved quality of life is due to freedom from dialysis, frequent blood sugar monitoring and insulin therapy, and by achieving euglycaemia, there may be fewer long-term complications of diabetes [7].

Despite the survival benefits, not all patients with type 1 diabetes mellitus and ESKD are suitable for SPK transplantation. The selection criteria for SPK transplantation in Australia and New Zealand are generally limited to younger recipients (typically less than 50 years), with a body mass index below 30 kg/m^2 and without severe untreated cardiac or peripheral vascular disease, amongst other criteria [7]. Those who are ineligible for SPK may opt to be listed on the deceased donor kidney list. Given the more stringent selection criteria for SPK recipients and greater use of expanded criteria donor (ECD) kidney organs amongst deceased kidney alone recipients over the past decade, there are few data with demonstrated comparability between SPK and deceased kidney alone patient groups, especially when accounting for inherent biases in waiting list times and patient co-morbidities [8,9]. Furthermore, it is uncertain whether older patients with type 1 DM and co-morbidities, who are ineligible for SPK transplantation, will accrue greater survival benefits with a deceased donor kidney transplant, compared to being on dialysis. Some patients who are ineligible for SPK may have the option of living donor kidney or PAK transplantation (commonly after receiving a living donor kidney graft). However, these remain less common; living donor kidney transplants accounted for 4.5% of transplant operations for type 1 diabetic patients in Australia and New Zealand from 2006 to 2016. Over this period, only nine PAK transplants were performed [10]. Given the scarcity of data for these transplant options, we therefore aimed to determine the survival and quality of life benefits of SPK and deceased donor kidney transplantation compared to patients on dialysis across different age categories in patients with type 1 diabetes mellitus requiring renal replacement therapy.

Materials and methods

Model structure and outcome measures

A decision analytic Markov model is a statistical method that can compare the risks and benefits of different strategies under conditions of uncertainty [11]. This method is useful when the optimal treatment strategy is unknown and when modelling the progression of a chronic disease over time. In this study, a probabilistic Markov model was built, where a hypothetical cohort (n = 10 000) was simulated though the model on the age-specific transition probability through mutually exclusive health states of dialysis and transplantation. The model consisted of five different treatment arms: (i) dialysis, (ii) deceased donor kidney transplantation, for recipients of all ages, (iii) deceased donor kidney transplantation, for recipients aged 50 years or younger, (iv) deceased donor kidney transplantation, for recipients aged over 50 years or (v) simultaneous pancreas–kidney transplantation for recipients aged under 55 years. Age stratification at 50 years was chosen for the deceased donor kidney transplant group to allow for comparison in baseline characteristics with SPK transplant recipients. The average incremental health gains were compared between SPK and dialysis arms, and between the deceased donor kidney transplantation and dialysis arms. The outcomes for treatment strategies were measured in terms of life years saved (LYS) and quality-adjusted life years (QALY). QALYs take into account both patient survival and health-related quality of life as patients transition through different health states (e.g. transitioning from being waitlisted on dialysis to receiving a kidney graft and being dialysis-free) [12]. Each health state is assigned a 'utility' ranging from 0 (death) to 1 (full health). Quality-adjusted life expectancy was calculated by assigning a utility to each health state and multiplying the utility by the time spent in that health state [12].

A schematic diagram of the Markov model structure is shown in Fig. 1 (full model in Appendix S1). The entire lifetime of the individual was modelled, whereby patients on dialysis were at risk of death at the end of each annual cycle. Among patients wait-listed for deceased donor kidney transplantation alone or SPK, the possible health states included the probability of receiving a kidney or SPK transplant, respectively, remaining on dialysis or death on dialysis. Once transplanted, SPK recipients could experience (i) survival with functioning grafts, (ii) death-censored graft failure (kidney graft failure requiring dialysis, pancreas graft

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failure requiring insulin therapy or combined graft failure requiring dialysis and insulin therapy) or (iii) death with a functioning graft. SPK-listed patients who remained on dialysis were at risk of death. For deceased donor kidney alone transplant recipients, they could experience survival with or without a functioning renal graft or death.

An annual cycle length was used, and a discount rate of 5% was applied to all outcomes. The models terminated when all potential recipients were deceased. The modelling was performed using TreeAge Pro version 2019 software (TreeAge Inc., Williamstown, MA, USA).

Input parameter estimates for the model

Clinical data

Probability for death on dialysis for type 1 diabetic patients was sourced from the Australian and New Zealand Dialysis and Transplant registry (ANZDATA) 2017 annual report, which includes analysis of data up to December 2016 [13]. All probabilities for deceased donor kidney transplant recipients were sourced from de-identified data from the ANZDATA registry (2006–2016). As ANZDATA does not include pancreas graft outcomes, SPK probabilities were sourced from the Westmead cohort of the Australia and New Zealand Islet and Pancreas Transplant Registry (ANZIPTR) (2006–2016), which is the largest pancreas transplant centre in Australia and New Zealand, and hold the most comprehensive data for pancreas graft management (e.g. type of exocrine drainage) and outcomes. The ANZDATA Registry holds the records of all patients on renal replacement therapy in Australia and New Zealand since 1964 [14]. It records the incidence, prevalence and outcome of dialysis and transplant treatment for patients with end-stage renal failure, with data collection occurring on a 6-month basis prior to 2004 and annually thereafter. The ANZIPTR registry holds records of all patients who receive islet and pancreas transplants performed in Australia and New Zealand (Westmead, Monash, Auckland and Adelaide) since 1984 [15]. Only SPK transplants with exocrine enteric drainage were included. Health utilities for each treatment option were obtained from a previous study using the Standard Gamble method (Appendix S2) [6].

Transition probabilities

Transition probabilities and their standard errors were derived from estimates calculated with cumulative incidence competing risk analysis. Cumulative incidence competing risk analysis was performed using package 'cmprsk' in R version 3.4.3 and was used to calculate the cumulative probability of the event (and corresponding standard error) at the last observation time. This probability was first converted to a rate, and rates to probability conversion were performed to obtain the

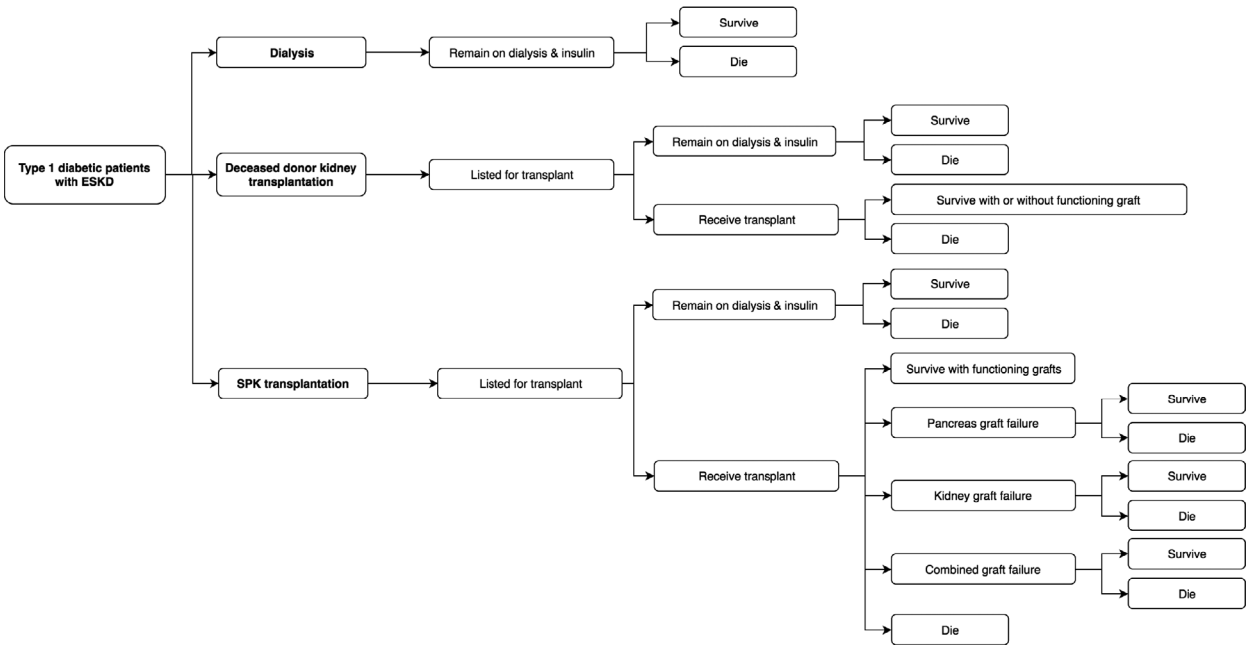

Figure 1 Schematic diagram of Markov model tree structure.

annual probability estimates, based on a constant event rate. The 95% confidence limits were taken as the upper and lower bound of the uniform probability distributions (Appendix S3).

Model assumptions

The model assumed that all transplant recipients were transplanted only once. The health states following transplantation were restricted to (i) survival with or without functioning graft or (ii) death, for deceased donor kidney recipients. Survival was restricted to with or without functioning deceased donor kidney graft given the sparsity of kidney graft failure events (Appendix S4). For SPK recipients, the model assumed that graft failure event only occurred once. Health states following either kidney graft failure or pancreas graft failure were restricted to survival without re-transplantation or death.

Sensitivity analysis

Sensitivity analyses were performed to test the robustness of the results to changes in the values of the variables. One-way sensitivity analysis was performed on each variable over a plausible range while holding all other variables constant. For the patient survival probability data, point estimates and upper and lower values of the 95% confidence interval were used for the sensitivity analysis. For the utilities associated with various health states, the range for the sensitivity analyses was as reported in the previous study [6]. Probabilistic sensitivity analysis was also undertaken by assigning uniform distributions to each model parameter for patient and graft survival outcomes. Using Monte Carlo simulation, each distribution was sampled to estimate the expected value of each treatment arm.

Results

Baseline characteristics of the cohort

During 2006–2016, there were 329 waitlisted patients with type 1 DM and end-stage kidney disease. Of these, 179 received an SPK transplant, 47 received a deceased donor kidney transplant, 11 received a living donor kidney transplant, nine received a PAK transplant, eight received 'other' transplants (pancreas transplantation alone (PTA) and transplants other than kidney or pancreas, e.g. liver), and 73 remained on dialysis. We excluded living donor kidney, PAK or 'other' transplantation types due to sample size and excluded patients with missing clinical data (mis-recorded dates of graft failure and patient death), with 299 patients included in the final analysis (Table 1, Fig. 2).

SPK transplant recipients were aged from 16 years to 53 years and were on average younger than deceased kidney recipients and those waitlisted on dialysis [mean age in years (95% CI) of 38.1 (33.9, 39.1), 48.9 (46.5, 51.2), 43.8 (41.5, 46.1), respectively]. Nine SPK recipients were aged between 50 and 53 years. The characteristics of dialysis patients being listed on the SPK and deceased donor kidney lists are shown in Appendix S4. All SPK transplant recipients had exocrine enteric drainage. SPK transplant recipients also had significantly fewer co-morbidities (chronic lung disease, cerebrovascular disease, peripheral vascular disease and coronary artery disease). However, recipients of SPK transplants spent similar time on the waitlist before transplantation compared to deceased donor kidney recipients [mean years (95% CI) of 1.0 (0.8, 1.1), 1.5 (1.1, 1.9), respectively].

Younger recipients (aged 50 years or younger) of deceased donor kidney alone transplantation had fewer co-morbidities compared to those older than 50 years (chronic lung disease 7.1% vs. 9.1%, peripheral vascular disease 28.6% vs. 48.5%, coronary artery disease 21.4% vs. 30.3%, respectively) (Appendix S6). The waiting time on dialysis was similar between the two age-groups, but the deceased donor age was lower for younger recipients compared to recipients aged over 50 years [means age in years (95% CI): 39.3 (33.4, 45.1) compared to 48.1 (42.9, 53.4)].

Overall graft failure and patient mortality events

Of the 73 patients remaining on dialysis, 24 (32.9%) died during a mean follow-up of 3.8 [95% CI 3.1, 4.5] years. Of the 47 deceased donor kidney recipients, 2 (4.3%) experienced kidney graft failure, and overall 8 (17.0%) died during a mean follow-up of 5.3 [95% CI 4.6, 6.1] years, with or without functioning graft. Of the 95 SPK recipients sourced from the Westmead cohort of ANZIPTR, there were 11 (11.6%) pancreas graft failure events, 7 (7.4%) kidney graft failure events and one combined pancreas–kidney graft failure event (1.1%). Ten (10.5%) SPK recipients died over a mean follow-up of 6.9 [95% CI 6.3, 7.6] years, of which 3 (3.2%) died after a graft failure event.

Comparative health benefits in life years saved

The average health benefit for dialysis, SPK transplantation and deceased kidney transplantation was 5.42 [95%

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Table 1. Baseline characteristics of the cohort.

	SPK recipients	Deceased kidney alone recipients	Dialysis patients	*P* value
Recipient demographics				
N	179	47	73	
Mean age in years (95% CI)	38.1 (33.9–39.1)	48.9 (46.5–51.2)	43.8 (41.5–46.1)	<0.001
Male (*n*, %)	103 (57.5)	34 (72.3)	41 (56.2)	0.147
Ethnicity (*n*, %)				
European Australians	173 (96.6)	41 (87.2)	61 (83.6)	0.029
First Nation Peoples	2 (1.1)	4 (8.5)	3 (4.1)	
Other	4 (2.2)	2 (4.3)	9 (12.3)	
Co-morbidities at time of first transplant (*n*, %)				
Chronic lung disease	9 (5.0)	4 (8.5)	8 (11.0)	0.303
Cerebrovascular disease	11 (6.1)	5 (10.6)	11 (15.1)	0.208
Peripheral vascular disease	47 (26.3)	20 (42.6)	31 (42.5)	0.066
Coronary artery disease	23 (12.8)	13 (27.7)	26 (35.6)	0.001
Mean years on dialysis (95% CI)	1.0 (0.8–1.1)	1.5 (1.1–1.9)	2.1 (1.7–2.6)	<0.001
Years on dialysis (*n*, %)				
0*	1 (0.6)	0 (0)	–	<0.001
>0–1	110 (61.5)	26 (55.3)	27 (37.0)	
>1–2	49 (27.4)	9 (19.1)	15 (20.5)	
>2	19 (10.6)	12 (25.5	31 (42.5)	
Immunological status				
Median HLA mismatches (IQR)	4 (3–5)	3 (2–5)		<0.001
Donor information				
Mean age (95% CI)	29.1 (27.4–30.8)	45.5 (41.3–49.7)		<0.001
Male (*n*, %)	101 (56.4)	28 (59.6)		0.698
Mean terminal creatinine in μmol/l (95% CI)	75.0 (70.1–79.9)	95.6 (73.6–117.6)		0.079
Transplant era (*n*, %)				
2006–2009	83 (46.4)	18 (38.3)		0.981
2010–2013	96 (53.6)	29 (61.7)		

*Waitlisted patients who were pre-emptively transplanted before commencing dialysis.

CI 5.41, 5.43], 10.90 [10.88, 10.92], 8.80 [8.78, 8.82] LYS, respectively (Table 2). Compared to being on dialysis, the average incremental health gains for SPK and deceased kidney transplantation were 5.48 [5.47, 5.49] and 3.38 [3.36, 3.40] LYS, respectively. The incremental health benefits for deceased kidney transplantation, compared to dialysis for recipients aged 50 years or younger, were 4.13 [4.10, 4.16] LYS and 3.05 [3.02, 3.08] LYS for those recipients older than 50 years.

The cumulative incremental gains in LYS for SPK and deceased donor kidney transplantation compared with being listed on dialysis are shown in Fig. 3a. Assuming the current waiting times for deceased donor kidney and SPK transplantation, and given that some SPK recipients were listed prior to starting dialysis, the survival benefits are observed at 2 years of waitlisting. All transplant recipients continued to gain survival benefits over the first 10 years since listing, with greatest benefits for SPK recipients, followed by deceased kidney recipients aged 50 years or younger, deceased kidney recipients of all ages and deceased kidney recipients older than 50 years.

Comparative health benefits in quality-adjusted life years

The average health benefit for dialysis, SPK transplantation and deceased kidney transplantation was 2.17 [95% CI 2.17, 2.17], 8.65 [8.64, 8.66], 4.64 [4.63, 4.65] QALY, respectively (Table 2). Compared to being on dialysis, the incremental health gains for SPK and deceased kidney transplantation were 6.48 [6.47, 6.49] and 2.46 [2.45, 2.47] QALY, respectively. When stratified by age, the incremental health benefits for deceased kidney transplantation for recipients aged 50 years or younger and recipients older than 50 years, compared to dialysis, were 2.99 [2.97, 3.01] and 2.25 [2.23, 2.27] QALY, respectively.

The cumulative incremental gains in QALYs for SPK transplantation compared to dialysis continue to rise

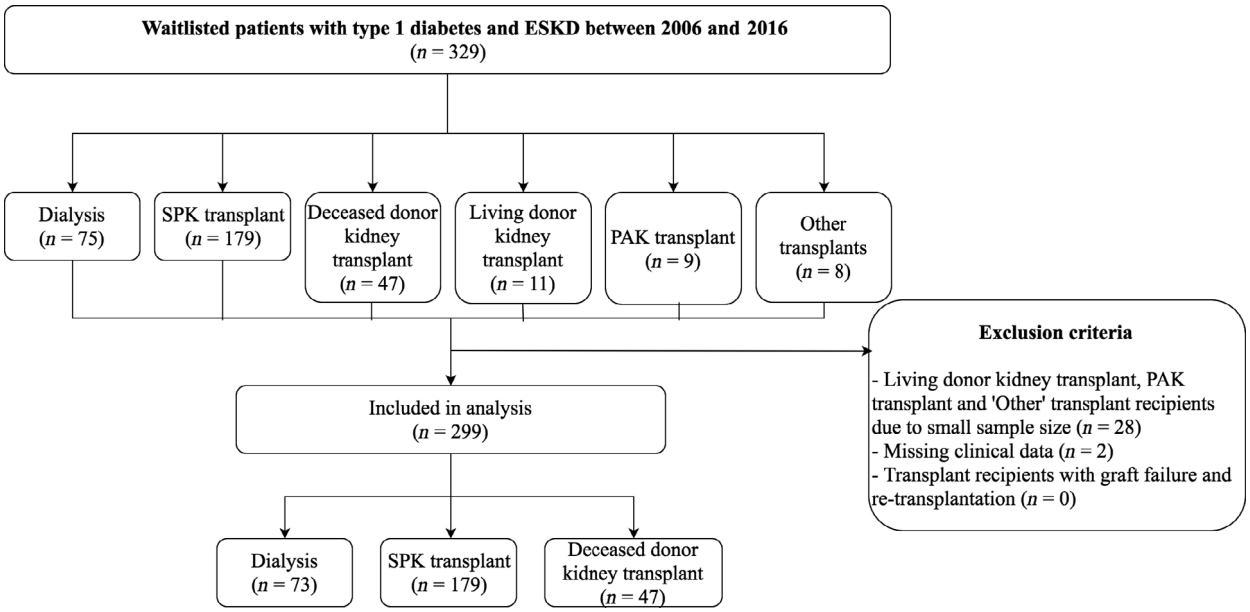

Figure 2 Patient flow diagram.

steadily after listing and reached 2.68 QALY at 10 years after listing (Fig. 3b). This compared to deceased donor kidney transplant recipients (all ages) who achieved modest gains in QALYs of 0.78 at 10 years after listing (0.73 and 0.97 QALY at 10 years after listing for deceased kidney recipients over 50 years and 50 years or younger, respectively), compared to listing on dialysis.

Sensitivity analysis

One-way sensitivity analysis was performed to assess the responsiveness of incremental health benefits (QALY) between two strategies to changes in each transition probability or utility. SPK transplantation and deceased kidney transplantation were compared against dialysis separately. The incremental tornado diagrams (Figs 4 and 5) summarize the results of the one-way sensitivity analyses. The expected value (EV) represents the incremental value (QALY) between the two strategies using the base case value for each parameter (as listed in Appendices S2 and S3). As the parameters deviate from their base case values, the incremental value changes. A 'black–white' bar signifies that incremental health benefits (QALY) increase as the parameter increases, while a 'white–black' bar signifies that the incremental health benefits (QALY) decrease as the parameter value increases.

For the incremental gains in QALYs for deceased donor kidney transplantation (comparator) against dialysis (baseline), 93% of the total uncertainty was accounted for by the utility associated with the dialysis-free-insulin-dependent health state, and the transition probabilities of death after deceased donor kidney transplant (with or without a functioning graft), and of receiving a deceased donor kidney transplant (Appendix S7). Varying these two transition probabilities individually over their 95% CI corresponded to a change in incremental gains of 1.58 QALY for the former and 1.03 QALY for the latter.

For SPK transplantation (comparator) against dialysis (baseline), incremental gains in QALYs were most sensitive to the following three transition probabilities: the probability of receiving a SPK transplant, annual mortality rates after SPK transplant with functioning grafts and annual graft failure rates after SPK transplant (61% of total uncertainty) (Appendix S8). Varying these parameters individually over their 95% CI corresponded to a change in incremental gains of 1.27, 0.98 and 0.84 QALY, respectively. An increase in the probability of receiving a SPK transplant, or a decrease in the latter two probabilities, led to an increase in incremental gains of QALYs among recipients of SPK transplants compared to dialysis.

Discussion

Using data from the recent era, our study findings reported substantial survival and quality of life benefits experienced by recipients of SPK transplant compared

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Table 2. Total and incremental health benefits of dialysis, deceased kidney transplantation and SPK transplantation.

	Total health benefits					Incremental health benefits*				
Effect	Dialysis	SPK transplantation	Deceased kidney transplantation, all ages	Deceased kidney transplantation, ≤50 YO	Deceased kidney transplantation, >50 YO	Dialysis	SPK transplantation	Deceased kidney transplantation, all ages	Deceased kidney transplantation, ≤50 YO	Deceased kidney transplantation, >50 YO
Average total health benefit, LYS [95% CI]	5.42 [5.41, 5.43]	10.90 [10.88, 10.92]	8.80 [8.78, 8.82]	9.55 [9.52, 9.58]	8.47 [8.44, 8.50]	ref	5.48 [5.47, 5.49]	3.38 [3.36, 3.40]	4.13 [4.10, 4.16]	3.05 [3.02, 3.08]
Average total health benefit, QALY [95% CI]	2.17 [2.17, 2.17]	8.65 [8.64, 8.66]	4.64 [4.63, 4.65]	5.17 [5.17, 5.19]	4.42 [4.40, 4.44]	ref	6.48 [6.47, 6.49]	2.46 [2.45, 2.47]	2.99 [2.97, 3.01]	2.25 [2.23, 2.27]

*Incremental health benefits of deceased kidney transplantation and SPK transplantation compared to dialysis.

to being on dialysis. The average incremental gains for SPK were 5.48 [5.47, 5.49] LYS and 6.48 [6.47, 6.49] QALY. SPK graft and patient survival outcomes have significantly improved over time owing to advances in surgical techniques, the introduction of tacrolimus, graft preservation techniques and better management of complications after transplantation such as prophylaxis for infections [16,17]. A review of US Organ Procurement and Transplantation Network data showed that three-year adjusted patient survival rates following SPK transplantation increased from 89.1% in 1997 to 93.4% in 2007 [18].

Deceased kidney transplantation also conferred considerable survival benefits compared to dialysis, although these were smaller, particularly in terms of quality-adjusted life years. Compared to dialysis, the average incremental gains from deceased donor kidney transplantation for type 1 diabetes were 3.38 [3.36, 3.40] LYS and 2.46 [2.45, 2.47] QALY. Thus, patients with type 1 diabetes and multiple co-morbidities, who are ineligible for SPK transplantation, also accrue greater survival benefits with a deceased donor kidney transplant compared to being on dialysis. However, the observed quality of life and survival gains are largely influenced by the age of the recipients. Younger recipients (aged 50 years or younger) experienced larger gains in LYS and QALY than older recipients (aged greater than 50 years) who had received a deceased donor kidney transplant.

The recent study by Esmeijer *et al.* [19] explored the relative survival benefits of transplantation compared with dialysis in patients with type 1 diabetes mellitus in a Dutch cohort. They found a considerable survival advantage for transplanted recipients (deceased or living donor kidney or SPK) compared to waitlisted patients on dialysis, with 5-year survival 76% vs. 32%, respectively. The benefits of deceased donor kidney transplantation for long-term survival and quality of life when compared to dialysis are well-established [20–23]. The survival advantage associated with kidney transplantation (compared with dialysis) extends even to patients with allograft failure and return to dialysis. Ortiz *et al.* [23] indicated a median survival of 15.7 years [95% CI 14.5–16.8] for patients who maintained kidney allograft function, 10.6 years [9.6, 11.7] for patients with kidney allograft failure and return to dialysis, and 2.2 years [2.0, 2.3] for those remaining on dialysis. Douzdijan *et al.*, Knoll *et al.* and Ong *et al.* have previously examined the relative benefits of SPK transplantation versus dialysis using decision analytic models [6,11,24]. By defining the various transition health states (e.g. from

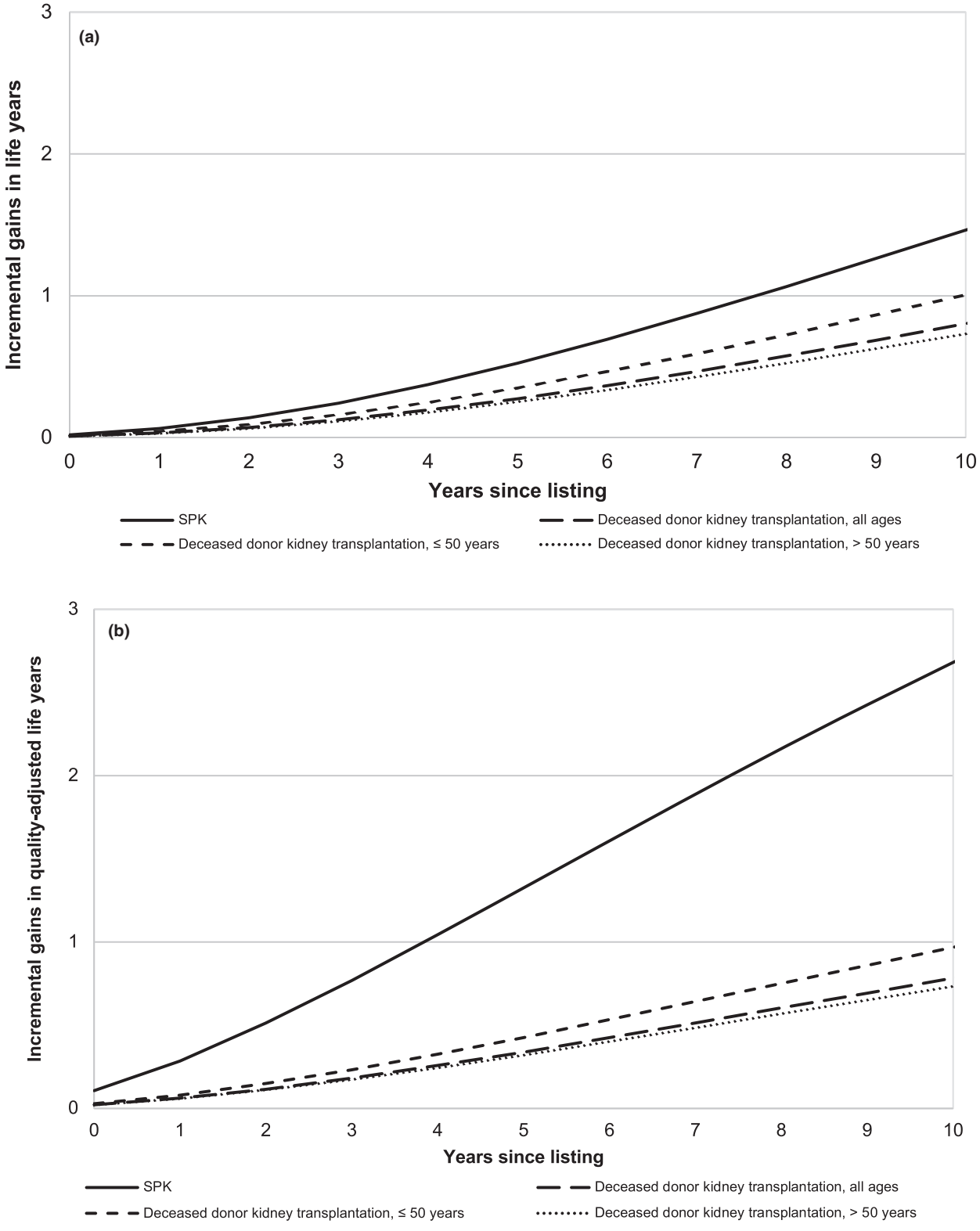

Figure 3 The cumulative incremental benefits of SPK and deceased donor kidney transplantation compared with being listed on dialysis, in (a) life years and (b) quality-adjusted life years.

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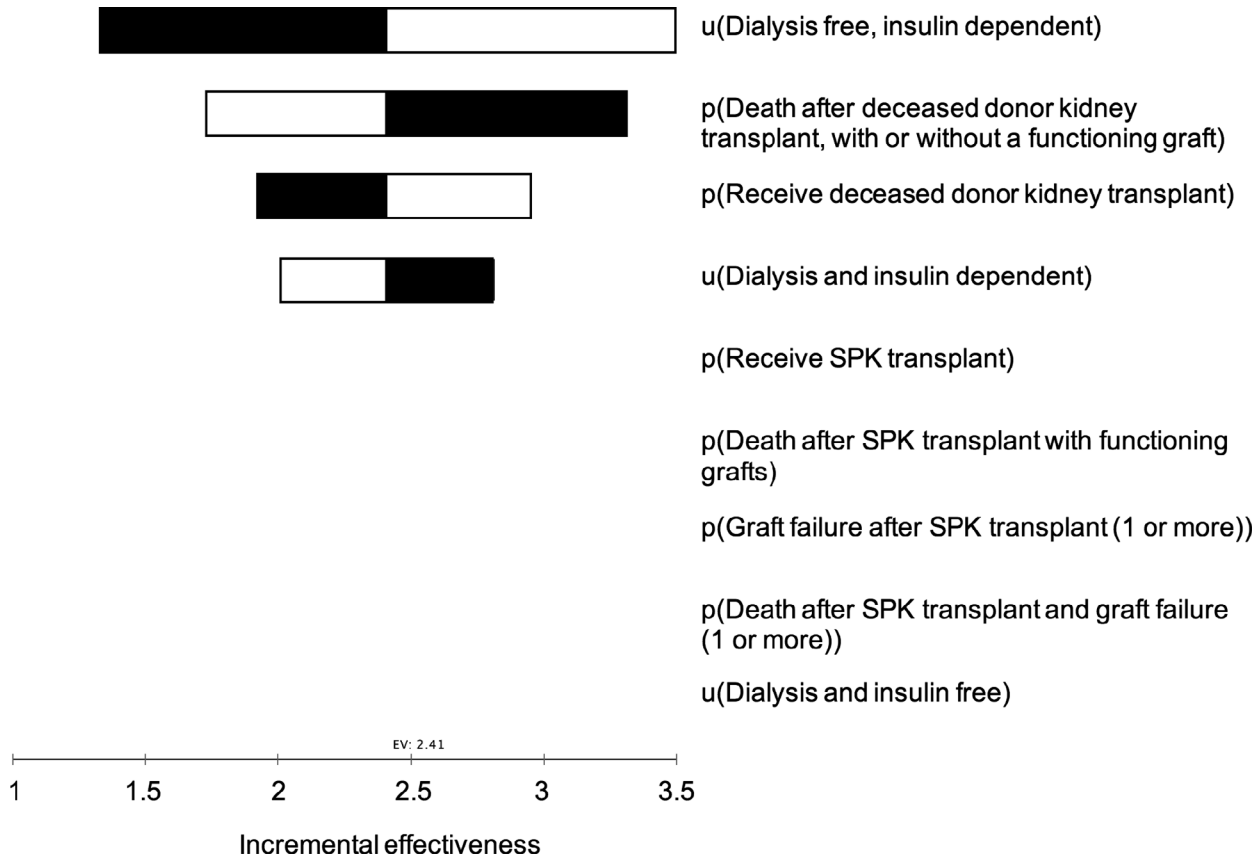

Figure 4 Tornado diagram for one-way sensitivity analysis, incremental effectiveness (QALY) for deceased kidney transplantation (all ages) vs. dialysis.

the time of waitlisting to graft loss), the use of decision analytic models captures the entire trajectory of the life course of a transplant recipient and allows for the simulation of longer-term post-transplant outcomes. Douzdijan *et al.* [6] found SPK transplantation yielded the best gains in QALY at five years (2.36), compared to deceased donor kidney alone transplantation (1.38) and dialysis (0.68) [24]. This has been corroborated by more recent data. Using a Markov model and input data from the United Network for Organ Sharing registry and the literature, Knoll *et al.* [11] found the incremental health benefits of SPK transplantation to be 7.92 LY and 4.57 QALY, compared to dialysis. Furthermore, using registry data from Singapore and the United States, Ong *et al.* [24] also found that SPK transplantation yielded the best QALY at five years (3.03), compared to deceased donor kidney alone transplantation (2.08) and dialysis (0.64). While the previous studies demonstrate the survival advantages of SPK transplantation over deceased donor kidney transplantation and dialysis, the present study also accounts for recipient age interactions and uses a probabilistic rather than a deterministic approach to determine the incremental benefits in life years and quality-adjusted LYS.

The extent of the survival benefits and quality of life gains with transplantation and listing is dependent on a number of variables. For both deceased kidney and SPK transplantation, one-way sensitivity analyses showed that survival benefits in QALYs compared to dialysis were most sensitive to the probabilities of receiving a transplant and death after transplantation. Thus, the main driver of incremental benefits is early transplantation. A small absolute difference of 6.5% in the probability of receiving an SPK transplant (i.e. 14.2–20.7%) corresponded with difference in expected QALY of 1.27 and accounted for 30% of risk. While on dialysis, patients not only have much poorer survival but also incur expensive dialysis costs [25]. Thus, outcomes are significantly improved if patients can be transplanted early in the course of their kidney disease progression [26]. However, the limited supply of donor organs means that the majority of SPK transplant patients are transplanted after they commence dialysis. Pancreas grafts from extended criteria donors, including donation

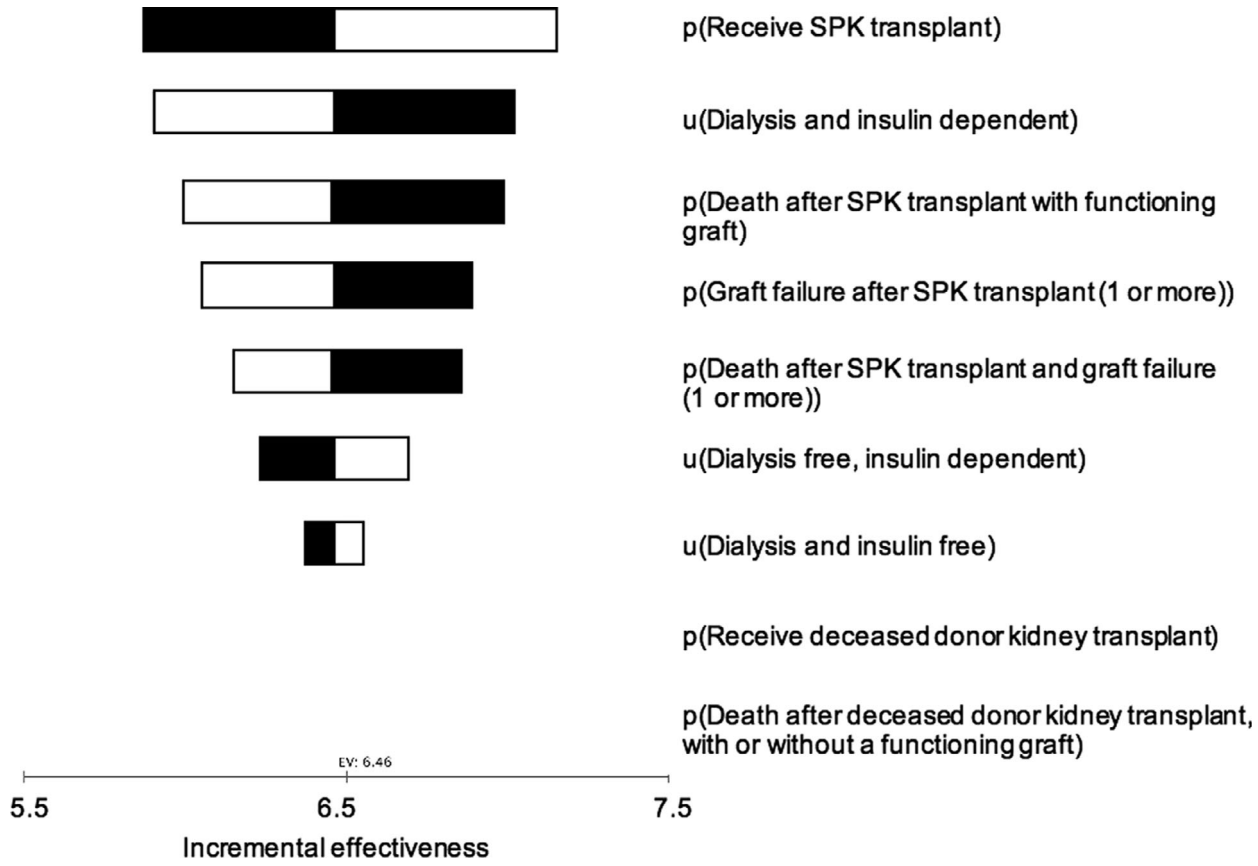

Figure 5 Tornado diagram for one-way sensitivity analysis, incremental effectiveness (QALY) for SPK transplantation vs. dialysis.

after circulatory death (DCD), are increasingly being used to improve the availability of donor organs by expanding the donor pool. Kidney donation after circulatory death is associated with more complications such as graft thrombosis [27], postoperative bleeding and delayed graft function [28,29]. However, promisingly, a recent meta-analysis comparing allograft survival in 152 DCD pancreas recipients and 1682 donor after brain death (DBD) pancreas recipients found that there was no significant difference in 10-year allograft survival, despite DCD pancreata having a higher incidence of early graft thrombosis [27]. Antemortem interventions such as heparinization may improve graft outcomes and warrant further study. Our sensitivity analyses indicated the impact of other variables on incremental effectiveness and expected nature of impact was largely insignificant.

A strength of our study is that it examines the survival benefits of SPK for type 1 diabetes using post-2006 data. Previous studies occurred in an era with exocrine bladder drainage for SPK transplantation, and different immunosuppressive therapies may not translate to contemporary clinical practice [5,6,24,30]. In recent years, bladder drainage has been superseded by enteric drainage, given that chronic exposure to pancreatic enzymatic secretions is associated with metabolic and urological complications in bladder drained organs [31,32]. The introduction of tacrolimus reduced the incidence of rejection and effectively facilitated the introduction of enteric pancreas exocrine drainage. Furthermore, T-cell-depleting agents and IL2-receptor blockers as induction therapies and the combined use of tacrolimus and mycophenolate mofetil for maintenance immunosuppression have also contributed to improved graft and patient survival outcomes [33]. Thus, this study affirms that SPK provides the best survival benefits for type 1 diabetic patients using contemporary data. We have also shown that deceased donor kidney transplantation still incurs significant survival benefits compared to dialysis in a selected group of potential candidates with type 1 diabetes mellitus.

Our study had some limitations. In the present study, the clinical and baseline characteristics of SPK and deceased donor kidney transplant recipient cohorts were dissimilar. As such, a direct comparison of the project gains in survival and quality of life between deceased

donor kidney and SPK transplantation could not be conducted. Our estimates of survival and QALYs gains are limited to patients for whom transplant clinicians had chosen to list and then transplant. It is probable that those who were transplanted may have fewer, or less severe, co-morbidities. Therefore, the outcome probabilities used in our models, which are based on actual outcomes, may over-estimate the benefits for those with more complex disease. The survival benefits of pancreas transplantation in recipients above 50 years of age could not be determined given our local eligibility criteria for SPK transplantation but has been previously analysed using German and US data [34,35]. We have not taken into consideration the benefits of living donor kidney transplantation or PAK transplantation due to insufficient sample size. The survival benefits of these transplant options in comparison to SPK have been analysed elsewhere [11,19,36,37]. In our modelling, we have not accounted for the potential benefits of re-transplantation.

To conclude, for younger patients with type 1 diabetes, SPK transplantation incurs the greatest survival gains compared to dialysis or deceased kidney donor transplantation. Older patients with type 1 DM and co-morbidities, who are ineligible for SPK transplantation, still accrue greater survival benefits with a deceased donor kidney transplant compared to being on dialysis.

Author contributions

RS, VC, JCC and GW: participated in research design. RS, VC and GW: participated in performance of the research and data analysis. All authors participated in writing of the paper.

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Conflicts of interest

Philip O'Connell reports grants and personal fees from CSL-Behring, personal fees from eGenesis, personal fees from Qihan Biotech, outside the submitted work; all other authors have no conflicts of interest to disclose as described by *Transplant International*.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Markov model tree structure.

Appendix S2. Utilities for health outcome states.

Appendix S3. Survival uniform probability distributions and weightings for types of SPK graft failure.

Appendix S4. Graft failure events for deceased donor kidney transplantation and SPK transplantation.

Appendix S5. Baseline characteristics of the dialysis patients waitlisted for SPK transplantation or deceased donor kidney transplantation.

Appendix S6. Patient baseline characteristics for deceased donor kidney transplant recipients stratified by age.

Appendix S7. One-way sensitivity analysis for the incremental effectiveness (QALY) for deceased kidney transplantation (all ages) vs dialysis.

Appendix S8. One-way sensitivity analysis for the incremental effectiveness (QALY) for SPK transplantation vs dialysis.

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